

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 015/04972	FOR FURTHER ACTION <small>see Form PCT/ISA/220 as well as, where applicable, item 5 below.</small>	
International application No. PCT/US05/44557	International filing date (day/month/year) 09 December 2005 (09.12.2005)	(Earliest) Priority Date (day/month/year) 04 May 2005 (04.05.2005)
Applicant IMPULSE DYNAMICS (ISRAEL), LTD.		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 2 sheets.



It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the Report

a. With regard to the **language**, the international search was carried out on the basis of:



the international application in the language in which it was filed.



a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))

b. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. ☐ **Certain claims were found unsearchable** (See Box No. II)

3. ☐ **Unity of invention is lacking** (See Box No. III)

4. With regard to the **title**,



the text is approved as submitted by the applicant.



the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,



the text is approved as submitted by the applicant.



the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the **drawings**,

a. the figure of the **drawings** to be published with the abstract is Figure No. _____



as suggested by the applicant.



as selected by this Authority, because the applicant failed to suggest a figure.



as selected by this Authority, because this figure better characterizes the invention.

b. ☒ none of the figures is to be published with the abstract.

INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER

IPC: A61N 1/00(2006.01);A61N 1/32(2006.01);C12N 13/00(2006.01);C12N 5/00(2006.01)

USPC: 607/2,50;435/173.1,375

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 607/2,50;435/173.1,375

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

MEDLINE, search terms: tissue, graft, stimulation, protein, gene

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	US 6,810,286 B2 (DONOVAN et al) 26 October 2004 (26.10.2004), entire document	1-76, 81-90, 97-133, and 149-154 ----- 93, 95
X --- Y	US 2004/0158289 A1 (GIROUARD et al) 12 August 2004 (12.08.2004), entire document	77, 78, 80 ----- 79
X --- Y	US 5,962,246 A (LADNER et al) 05 October 1999 (05.10.1999), column 12, lines 8-11 and 58-60.	91, 92, 94, 96, 134-148 ----- 93, 95

☐ Further documents are listed in the continuation of Box C.

☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T"

later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X"

document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y"

document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&"

document member of the same patent family

Date of the actual completion of the international search

28 April 2006 (28.04.2006)

Date of mailing of the international search report

12 MAY 2006

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

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Authorized officer

For Robert E Pezzuto

Telephone No. 571-272-3766

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:
WILLIAM H. DIPPET
WOLF, BLOCK, SCHORR & SOLIS-COHEN LLP
250 PARK AVENUE
NEW YORK, NY 10177

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43bis.1)

Applicant's or agent's file reference 015/04972		Date of mailing (day/month/year) 12 MAY 2006 FOR FURTHER ACTION See paragraph 2 below	
International application No. PCT/US05/44557	International filing date (day/month/year) 09 December 2005 (09.12.2005)	Priority date (day/month/year) 05 May 2005 (05.05.2005)	
International Patent Classification (IPC) or both national classification and IPC IPC: A61N 1/00(2006.01);A61N 1/32(2006.01);C12N 13/00(2006.01);C12N 5/00(2006.01) USPC: 607/2,50;435/173.1,375			
Applicant IMPULSE DYNAMICS (ISRAEL), LTD.			

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☒ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

8/12/06

Name and mailing address of the ISA/ US Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (571) 273-3201	Date of completion of this opinion 28 April 2006 (28.04.2006)	Authorized officer For Robert E Pezzuto <i>Virginia Libby</i> Telephone No. 571-272-3700
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**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.

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Box No. I Basis of this opinion

1. With regard to the language, this opinion has been established on the basis of:

- ☒ the international application in the language in which it was filed
- ☐ a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

2. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

a. type of material

- ☐ a sequence listing
- ☐ table(s) related to the sequence listing

b. format of material

- ☐ on paper
- ☐ in electronic form

c. time of filing/furnishing

- ☐ contained in the international application as filed.
- ☐ filed together with the international application in electronic form.
- ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

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Box No. V Reasoned statement under Rule 43 *bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims <u>79</u>	YES
	Claims <u>1-78 and 80-154</u>	NO
Inventive step (IS)	Claims <u>NONE</u>	YES
	Claims <u>1-154</u>	NO
Industrial applicability (IA)	Claims <u>1-154</u>	YES
	Claims <u>NONE</u>	NO

2. Citations and explanations:

Please See Continuation Sheet.

**WRITTEN OPINION OF THE
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Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

Claim 46 objected to under PCT Rule 66.2(a)(iii) as containing the following defect(s) in the form or contents thereof: The claim lacks reference to the claim from which it depends. The claims states "a method according to", but does not specify from which claim it depends.

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Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

V. 2. Citations and Explanations:

Claims 1-76, 81-90, 97-133, and 149-154 lack novelty under PCT Article 33(2) as being anticipated by Donovan et al. (U.S. Patent No. 6,810,286), herein Donovan.

Regarding claims 1-74, 81-90, 97-120, 129, 130, and 149-154, Donovan discloses a stimulation device which applies an electric field to the heart of a patient in order to modify the activity of cardiac proteins and treat conditions such as coronary artery disease and ischemia (see col. 2, ln. 19-26). The device includes at least one electrode 3 applied to in vivo tissue and a controller 1 to control delivery of stimulation to the tissue (see Figure 1). It is inherent that the modified proteins are not sensitive to physiologically occurring inter-cellular electric fields, otherwise the electrical therapy would be unnecessary. The electrical energy applied by Donovan acts to enhance angiogenesis in order to repair the heart and ensure that oxygen is adequately supplied to the body. Donovan discloses that the electrical energy is applied at a subthreshold level in order to prevent excitation of the heart tissue (see col. 2, ln. 27-28). The method taught by Donovan is inherently capable of being applied to any number of tissue forms, including a tissue sample, in vivo tissue, separated cells, and tissue homogenate. Further, Donovan discloses programming the device to apply stimulation at a level which produces a desired effect and measuring the effect the stimulation has on the tissue sample (see Claim 28).

Regarding claims 75 and 76, the pulse sequence delivered by Donovan is chosen in order to have the greatest effect on the desired protein activity modification to treat coronary artery disease and the controller is programmed to carry out the prescribed stimulation parameters (see col. 9, ln. 23-44).

Regarding claims 121-123 and 128, it is inherent within the method of Donovan that when the electrodes are placed on the heart of the patient, either transvenously or non-transvenously, a testing procedure must be enlisted in order to ensure that the placement of the electrodes is suitable for applying the desired stimulation.

Regarding claims 124-127 and 131-133, Donovan discloses that the therapy is applied to the heart of the patient and the location of the stimulation is based on the desired effect of the stimulation therapy (see col. 9, ln. 9-17). Further, Donovan discloses that the stimulation therapy may be applied in order to treat ischemia (see col. 1, ln. 32-33).

**WRITTEN OPINION OF THE
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Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Claims 77, 78, and 80 lack novelty under PCT Article 33(2) as being anticipated by Girouard et al. (U.S. 2004/0158289), herein Girouard. Girouard discloses a method for conditioning living tissue through electrical therapy which includes providing tissue samples (plugs), applying an electric field to the samples, and implanting the samples into a patient (see paragraph 74). Further, the tissue utilized by the Girouard is disclosed to be cardiac tissue (see paragraph 39, ln. 1-6). The cell therapy which is administered to the tissue in block 110 constitutes genetic modification of the tissue being treated (see Figures 1 and 2).

Claims 91-96, and 134-148 lack novelty under PCT Article 33(2) as being anticipated by Ladner et al. (U.S. Patent No. 5,962,246), herein Ladner. Ladner discloses a biochemical assaying kit for determining biochemical activity in relation to biochemical markers associated with genes, which includes an indicator of protein phosphorylation (see col. 12, ln. 58-60). The kit of Ladner is disclosed to be used to determine the changes in the proliferation status of a tissue due to various stimuli, including electrical stimulation (see col. 12, ln. 8-11 and 50-51), therefore it is inherent that the kit includes instructions for using phosphorylation as an indicator of tissue state. Further, Ladner discloses indicators for protein or mRNA expression levels (see col. 15, ln. 43-58).

Claim 79 lacks an inventive step under PCT Article 33(3) as being obvious over Girouard. Girouard discloses the claimed invention except for the excision of the plugs from a same heart into which they are later implanted. However, it is well known in the field of tissue engineering to explant a tissue plug from a patient, treat it either through electrical stimulation or drug therapy, and re-implant it into its original location.

Claims 1-154 meet the criteria set out in PCT Article 33(4), and thus have industrial applicability because the subject matter claimed can be made or used in industry.

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under Article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the *PCT Applicant's Guide*, a publication of WIPO.

In these Notes, "Article," "Rule" and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions, respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g., the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Preliminary Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When? Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How? Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.